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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,601	06/23/2005	Benito Munoz	MS0018YP	4252

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	**PAPER NUMBER**
1626	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,601	MUNOZ ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21 and 31-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *21,32,37-40 and 42* is/are allowed.

6)☒ Claim(s) *20,31,33-36 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/20/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 20, 21 & 31-42 are pending in the instant application. **Claims 20, 31, 33-36 & 41** stand rejected. No amendments are presented.

Information Disclosure Statement

Applicants' information disclosure statement (IDS), filed on 06/20/2007 has been considered. Please refer to Applicants' copy of the 1449 submitted herein.

Response to Arguments

Applicant's arguments filed 06/20/2007 have been fully considered but they are not persuasive. Applicant argues that the specification as filed sufficiently enables one skilled in the art to use the invention commensurate with the scope of said rejected claims. Pointed out by Applicant: one skilled in the art can readily identify patients in need of treatment for preventing, delaying or reversing the progression of Alzheimer's Disease; and, after identifying patients in need of said treatment, an Aβ42 lowering agent can be administered to the patient to prevent, delay or reverse the progression of Alzheimer's Disease.

In response, Examiner acknowledges the following findings:

1) Alzheimer's Disease (AD) is a neurodegenerative disease characterized by progressive cognitive deterioration, declining activities of daily living, neuropsychiatric symptoms, and/or behavioral changes. Plaques which contain misfolded proteins, called *beta amyloid*, form in the brain many years before the clinical signs of AD are

observed. Together, these plaques and neurofibrillary tangles form the pathological hallmarks of the disease. These features can only be discovered at autopsy and medications can help reduce the symptoms of the disease, but they cannot change the course of the underlying pathology.

2) It is accepted that Aβ42 is believed to be the main culprit in the pathogenesis of AD, (*see* Weggen *et al. Nature* **2001**, IDS).

3) The compounds of the present invention demonstrated to preferentially lower the levels of Aβ42 relative to the level of Aβ40 utilizing the assay as described in the specification, (pages 25-6).

4) Analogous non-steroidal anti-inflammatory drugs (NSAIDs) have also been demonstrated to lower levels of amyloid plaque buildup in the brain, (*see* Weggen *et al. Nature* **2001**, IDS).

5) Many questions remain to be answered. The compounds of the present invention demonstrated to preferentially lower the levels of Aβ42, but can they *prevent* plaque build-up? Would preventing amyloid plaque build-up translate to preventing AD? Do NSAIDs affect disease progression and, if so, by what mechanism? Will lowering amyloid burden translate into cognitive stabilization or even improvement? (*see* Citron *et al. Nature* **2004**, p. 684, cited in previous Office Action). Does reducing amyloid plaque build-up change the ultimate outcome (patient ultimately dies of AD)? In other words, has the science evolved such that the disease itself is being treated or are only the symptoms being treated?

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20, 31, 33-36 & 41 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for a method for the treatment of Alzheimer's disease, does not reasonably provide enablement for a method for preventing, delaying or reversing the progression of Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

In re Wands, 8 USPQ2d 1400 (1988), discusses the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1. ***The nature of the invention;***
2. ***The state of the prior art;***
3. ***The predictability or lack thereof in the art;***
4. ***The amount of direction or guidance present;***
5. ***The presence or absence of working examples;***
6. ***The breadth of the claims;***
7. ***The quantity of experimentation needed; and***
8. ***The level of skill in the art***

each of which is discussed in turn below.

The nature of the invention

The nature of the invention is a method for the treatment of Alzheimer's disease comprising administering to a patient a compound of the Formulae I or I'.

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. *In the instant case*, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and compositions may provide a treatment for Alzheimer's disease, but it does not mean that the same group of compounds and compositions may prevent, delay or reverse the progression of Alzheimer's disease.

From a recent review by Citron (*Nature Reviews Neuroscience* **2004**, *5*, 677-685): Alzheimer's disease (AD) affects more than 12 million individuals worldwide, and

death occurs, on average, within nine years of diagnosis. The current standard of care for mild to moderate AD includes treatment with acetylcholinesterase inhibitors, and an NMDA antagonist has recently been approved for the treatment of advanced AD in the US. Two main disease mechanism-based approaches, which have been studied for more than 10 years, are based on the involvement of two proteins, amyloid-β (Aβ) and tau, in AD pathology. Aβ is the main constituent of senile plaques, one of the key pathological characteristics of AD. Genetic and pathological evidence strongly supports the amyloid cascade hypothesis of AD, which states that amyloid- β42 (Aβ42), a proteolytic derivative of the large transmembrane protein amyloid precursor protein, has an early and vital role in all cases of AD. The most direct approach in anti-amyloid therapy is the reduction of Aβ42 production.

The amount of direction or guidance present and the presence or absence of working examples

There is no direction or guidance provided which supports Applicant's claimed method for preventing, delaying or reversing the progression of Alzheimer's disease as indicated. The direction or guidance present in Applicants' Specification for a method of using the compounds of Formulae I and I' to treat Alzheimer's disease include the *Assays for Determining Biological Activity* (Protocol for measuring Aβ1–40 and Aβ1-42 levels) is found on pages 25-26.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 20, 31, 33-36 & 41 are drawn to a method for preventing, delaying or reversing the progression of Alzheimer's disease. In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention.

In the instant case, Applicant states: "that one skilled in the art can readily identify patients in need of treatment for preventing, delaying or reversing the progression of Alzheimer's Disease." Applicant further states that Examiner is requiring an overly strict standard for enablement that it would be necessary to demonstrate that the identified subject did not develop the disease. However, Examiner points out that the ultimate cause of the disease is unknown. Current drugs improve symptoms, but do not have profound disease-modifying effects. No medical tests are available to diagnose Alzheimer's disease conclusively pre-mortem. Expert clinicians who specialize in memory disorders can now diagnose AD with an accuracy of 85–90%, but a definitive diagnosis of Alzheimer's disease must await microscopic examination of brain tissue, generally at autopsy. Therefore, an undue quantitiy of experimentation is necessary (as pointed out by Citron *et al.*) to demonstrate that NSAIDs work in a large scale clinical trial, followed further by years of observating patients to determine if the disease is actually prevented.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. Canceling **Claims 20, 31, 33-36 & 41** would overcome this rejection.

Allowable Subject Matter

Claims 21, 32, 37-40 & 42 are free of the prior art; nothing known anticipates or renders said claims obvious. As discussed above, the most direct approach in anti-amyloid therapy is the reduction of Aβ42 production, an approach that has been studied for over ten years. A structure and keyword search revealed that no compounds have been published that are implicated as anti-amyloid compounds.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Date: August 21, 2007